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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 10/751,342
Filing Date: December 31, 2003
Appellant(s): WEERS ET AL.

Guy V. Tucker
Reg. No. 45,302
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed November 24, 2010 appealing from the
Office action mailed May 24, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:
1-15, 18-20, 23-25, 28-31, 38-40, 63-78, 98, 99 and 101.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

4,950,477	Schmitt et al.	08-1990
6,395,300 B1	Straub et al.	05-2002
2002/0177562 A1	Weickert et al.	11-2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-15, 18-20, 23-25, 28-31, 38-40, 98 and 99 are rejected on the ground of nonstatutory obviousness-type double patenting as being

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unpatentable over claims 23-25, 27-30, 35-44 of copending Application No. 11/187,757 ('757) in view of Straub et al. (US 6,395,300 B1) in further view of Schmitt et al. (US 4,950,477).

Although the conflicting claims are not identical, they are not patentably distinct from each other. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Application '757 teaches a method for treating a patient suffering from a fungal infection of the lung, comprising administering to the patient a therapeutically effective amount of a pharmaceutical formulation comprising a lipid matrix and at least one particle of an antifungal agent in the lipid matrix wherein the aerosolized (see claim 35) pharmaceutical formulation is for pulmonary administration (see claim 45) via inhalation (see claims 23 and 27). For clarification, the application '757 defines treating as providing prevention of a particular condition (see page 2, paragraph 26, lines 6-8). The lipid matrix comprises a phospholipid (see claim 7). The composition can be a dry powder that has a bulk density of less than 0.5 g/cm^3 . The antifungal agent is amphotericin B (see claims 29 and 30). The amount of antifungal agent is at least twice the minimum inhibitory concentration of the antifungal agent for at least one week (see claim 35), three weeks or three months (see claims 39-42). Thus, determining the minimum inhibitory concentration is taught Tarara et al. because in order to administer twice the minimum inhibitory concentration, the minimum inhibitory concentration of the

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antifungal agent needs to be determined. The minimum inhibitory concentration is in the epithelial lining or the solid tissue of the lung (see claims 36 and 37), with a lung concentration at least 9 $\mu\text{g/g}$ or in the range of 9 $\mu\text{g/g}$ to 15 $\mu\text{g/g}$ (see claims 43 and 44). No active agent is detectable in the patient's serum or organs subsequent to administration of the formulation (see claims 31-34). The minimum inhibitory concentration is the minimum inhibitory concentration in the epithelial lining or solid tissue of the lung (see claims 36 and 37).

The application '757 does not teach a single dose or two doses of the pharmaceutical formulation during the first week of administration (claims 8 and 9). The two period administration wherein the antifungal agent is administered more frequently or at a higher dosage during the first period than during the second period is also not taught (claim 10). Neither is the administration comprising delivering the formulation periodically to maintain the antifungal agent lung concentration taught (claim 13). '757 also does not teach that the powder is a porous particle (claims 1 and 23), or that the specific fungal infection treated is aspergillosis (claims 23, 98 and 99).

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of '757 and the administration detailed above in the applicant's claims 8, 9, 10 and 13 and determining the minimum inhibitory concentration of an antifungal agent for inhibiting pulmonary fungal growth because of the following: (1) the antifungal agent is administered for at least one week, three weeks or three

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months to maintain the twice the minimum inhibitory concentration (see claims 35 and 40); (2) it is within the art to administer a drug several times during a treatment. In order to treat the fungal infection the antifungal agent must be present in concentrations that are effective. Whether the drug is administered once, twice, or several times, the important factor is that twice the minimum inhibitory concentration is maintained in the lungs.

Straub et al. teaches low aqueous solubility drugs such as the anti-fungal drug amphotericin B in a porous matrix form to provide a faster rate of dissolution following administration to a patient, as compared to non-porous matrix forms of the drug (see abstract, lines 1-2 and 15-18 and column 4, lines 47-48). The preferred embodiment is for oral administration using a dry powder inhaler for pulmonary administration (see column 3, lines 1 and 6-8).

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of '757 and wherein the powder is porous because Straub et al. teaches that a porous matrix of the antifungal agent amphotericin B provides a faster rate of dissolution following administration to a patient as compared to non-porous forms of the drug (see abstract, lines 1-2 and 15-18 and column 4, lines 47-48).

Schmitt et al. teaches a method of treating pulmonary aspergillosis by administering amphotericin B in an aerosol spray (see abstract).

To one of ordinary skill in the art at the time of the invention would have found it obvious to combine the method of '757 and wherein the specific fungal infection treated is aspergillosis because Schmitt et al. teaches that amphotericin B treats aspergillosis (see abstract).

Claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-76, 98, 99 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weickert et al. (US 2002/0177562 A1) in view of Straub et al. (US 6,395,300 B1).

Weickert et al. teach a dry powder aerosolized polyene composition for oral inhalation to the lung to treat pulmonary and systemic fungal infections (see abstract; example 1; and page 10 paragraph 114; addresses claims 1, 20, 23, 40, 63, and 76) such as aspergillosis (see paragraph 125, addresses claims 23, 98 and 99). The composition comprise an antifungal agent such as amphotericin B (see example 1, addresses claims 11, 15, 23, 67, 71) in concentrations of about 0.01 mg/kg to about 7 mg/kg per dose 1 to 8 times daily over a course of from about 7 to about 183 days (see page 11, paragraph 127; addresses claims 1, 4-9, 12, 13, 23, 28, 29-31, 63, 66 and 68-70). Typically the composition is administered in doses that are 3-10 times or more times the MIC of the causative fungal pathogen. Depending upon the particular

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antifungal compound, the condition being treated, the age and weight of the subject and the like, the dosage amount can vary (see page 11, paragraph 128, addresses claims 1, 12, 14, 23, 62 and 63). The compositions penetrate into the airways of the lungs and achieve effective concentrations in the infected secretions and lung tissue, including the epithelial lining fluid, alveolar, macrophages, and neutrophils, typically exceeding the MIC's of most respiratory fungal pathogens (see paragraph 124, addresses claims 2, 3, 24, 25, 64 and 65). The composition may also contain phospholipids (see paragraph 83; addresses 18, 19, 38, 39, 74 and 75). The powder particle size is below 3.3 microns and a bulk density of from about 0.05 to 10 g/cubic centimeter (see paragraphs 112 and 113; addresses claims 1, 23 and 72). The aerosolized inhaler can be delivered in a variety of different devices that involve a valve to release the formulation (see paragraph 118-120; addresses claim 77), such as a pressurized metered dose inhaler containing a solution or suspension of the drug in a propellant such as CFC, HFC or fluorocarbon (see paragraph 121; addresses claim 78). The formulations are particularly useful for immunocomprised patients such as individuals undergoing chemotherapy, organ transplant recipients, or suffering from HIV (see paragraph 125, addresses claim 63).

Weickert et al. does not specifically teach wherein the pharmaceutical formulation comprises porous particles (claims 1, 23 and 73), or wherein the formulation is administered in a first dosage followed after a predetermined time interval by a second dosage that is greater than the second dosage (claim 1). Weichert et al. also

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does not teach wherein the administration comprises a first administration period and a second administration period wherein the amphotericin B is administered more frequently or at a higher dosage during the first administration period than during the second administration period (claim 23). Weichert et al. also does not specifically teach the administration of an immunosuppressive agent (claim 63), or an administration comprising delivering at least two doses per week of the pharmaceutical formulation before the administration of the immunosuppressive agent and wherein the target concentration is maintained by administering doses of the pharmaceutical formulation less frequently as disclosed in claim 66. Weichert et al. also does not specifically teach that after two days following administration, a concentration of antifungal agent in the lungs is at least about 150 times a concentration of antifungal agent in the lungs delivered intravenously, and wherein a concentration of antifungal agent in the serum is substantially zero (claim 101). Weichert et al. also does not teach that the MIC was specifically determined (claims 1, 23 and 63)

Straub et al. teaches low aqueous solubility drugs such as the anti-fungal drug amphotericin B in a porous matrix form to provide a faster rate of dissolution following administration to a patient, as compared to non-porous matrix forms of the drug (see abstract, lines 1-2 and 15-18 and column 4, lines 47-48). The preferred embodiment is for oral administration using a dry powder inhaler for pulmonary administration (see column 3, lines 1 and 6-8). The matrix further includes a pegylated excipient, such as pegylated phospholipic to shield the drug from macrophage uptake, which prolongs its

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half-life or enhance bioavailability of the drug (see column 2, lines 63-67). The density of the dry porous matrix powder is preferably less than 0.8 g/mL to provide sufficient surface area to enhance wetting of the dry porous matrix and enhance drug dissolution (see column 3, lines 65-66 and column 4, lines 2-5).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Weickert et al. and wherein the pharmaceutical formulation comprises hollow and/or porous particles within a matrix material that comprises one or more phospholipids because Straub et al. teaches the following: (1) drugs such as the anti-fungal drug amphotericin B in a porous matrix form to provide a faster rate of dissolution following administration to a patient, as compared to non-porous matrix forms of the drug (see abstract, lines 1-2 and 15-18 and column 4, lines 47-48); (2) the density of the dry porous matrix powder is preferably less than 0.8 g/mL to provide sufficient surface area to enhance wetting of the dry porous matrix and enhance drug dissolution (see column 3, lines 65-66 and column 4, lines 2-5); and (3) the matrix further includes a pegylated excipient, such as pegylated phospholipic to shield the drug from macrophage uptake, which prolongs its half-life or enhance bioavailability of the drug (see column 2, lines 63-67). Thus, it would be beneficial for the methods and compositions of Weickert et al. to comprise hollow and/or porous particles within a matrix material that comprises one or more phospholipids because of the reasons stated above.

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Weickert et al. wherein the administration of the formulation is as those disclosed in claims 1, 23 and 63, or the specific dosage amounts disclosed in claims 12-14, 23 and 68-70 because of the following teachings: 1) Weickert et al. teach that depending upon the particular antifungal compound, the condition being treated, the age and weight of the subject and the like, the dosage amount can vary (see page 11, paragraph 128, addresses claims 1, 12, 14, 23, 62 and 63); and 2) It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, it is within the skill of the art to design an administration schedule and or amounts depending on the information given above.

In regards to the administration of an immunosuppressant agent, it would be obvious to administer such an agent because Weickert et al. teach that the formulations are idea for those who are undergoing chemotherapy, organ transplant recipients, or suffering from HIV (see paragraph 125). Thus, since these patients are most likely taking immunosuppressant agents, it is within the skill of the art to determine a an administration schedule and or amounts depending upon the particular antifungal compound, the condition being treated, the age and weight of the subject and the like.

In regards to claim 101, the teaching of Ponikau in view of Straub et al. render these claims obvious because Ponikau teaches the applicant's administration method and Straub et al. teaches that applicant's claimed drug (amphotericin B) can be delivered in a porous aerodynamic powder via inhalation to the lungs. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). Therefore administering the same drug in the same manner will give the same properties.

(10) Response to Argument

The Appellant argues that Weickert et al. does not disclose or suggest the following: 1) the administration of a sufficient amount of a formulation to maintain for at least one week a target antifungal lung concentration of at least two times a determined minimum inhibitory concentration; 2) administration of a first dosage and then a second dosage less than the first dosage (i.e. treatment regimen); and 3) porous particles having a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm³. It is the discovery and recognition that it is the maintenance of the lung concentration over a period of at least one week that is a significant advancement in the art over the teachings of Weickert et al.. Weickert et al.'s administration technique where the lung concentration of antifungal agent may spike above the 2x minimum inhibitory concentration and then fall below the threshold is neither as effective as Appellant's claimed methodology. Further, there is no teaching in Weickert et al. to vary the dosage for the same patient within the same treatment regimen. Additionally, nowhere

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does Weickert et al. teach that dissolution of a drug is an issue to incorporate the teaching of Straub et al. Straub et al. and Schmidt et al. do not teach these limitations either. Appellant argue that the Examiner used Ponikau and Straub et al. in view of Gomez et al. to reject claims 77 and 78, but nether of the references teach the limitations of the claims.

The Examiner disagrees because first, Weickert et al. teaches an administration of a sufficient amount of a formulation to maintain for at least one week a target antifungal lung concentration of at least two times a determined minimum inhibitory concentration with the following teachings: 1) Weickert et al. teach a dry powder aerosolized polyene composition for oral inhalation to the lung to treat pulmonary and systemic fungal infections (see abstract; example 1; and page 10 paragraph 114) such as aspergillosis (see paragraph 125); 2) the composition comprise an antifungal agent such as amphotericin B (see example 1) in concentrations of about 0.01 mg/kg to about 7 mg/kg per dose 1 to 8 times daily over a course of from about 7 to about 183 days (see page 11, paragraph 127); and 3) typically the composition it administered in doses that are 3-10 times or more times the MIC of the causative fungal pathogen.

In regards to the administration regimen disclosed in claims 1, 23 and 63 or the specific dosage amounts disclosed in claims 12-14, 23 and 68-70, one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Weickert et al. and the claimed administration regimen because of the following teachings: 1) Weickert et al. teach that depending upon the particular antifungal compound, the condition being treated, the age and weight of the subject and the like, the dosage amount can vary (see page 11, paragraph 128); and 2) It is noted

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that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In *re* Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, it is within the skill of the art to design an administration schedule and or amounts depending on the information given by Weickert et al. Weickert et al. teaches drug concentration amounts and general administration such as about 0.01 mg/kg to about 7 mg/kg per dose 1 to 8 times daily over a course of from about 7 to about 183 days (see page 11, paragraph 127). It is within the skill of the art to determine a specific treatment regimen depending on the condition, drug, age, and weight of the patient. Therefore, if the patient has a severe case of an infection, a more vigorous dosage regimen may be prescribed. The fact that the dosage can be administered up to 8 times daily for more than a week, and that each dosage is 3-10 or more times the MIC of the causative fungal pathogen, it would be obvious that the dosage is maintained for at least one week.

In regards to the porous particles having a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm³, one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the method of Weickert et al. and a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm³ because Weickert et al. teach the powder particle size is below 3.3 microns and a bulk density of from about 0.05 to 10 g/cubic centimeter (see paragraphs 112 and 113). Straub provides the motivation to provide a porous matrix. Particularly, Weickert et al.

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does not have to list dissolution problems for incorporation of the Straub et al. teachings to be used. One skilled in the art would appreciate that the faster the drug is dissolved and absorbed into the body, the faster the treatment can begin and/or be maintained.

In regards to the arguments of claims 77 and 78, the Examiner has rejected these claims over Weickert et al. in view of Straub et al. Particularly, Weickert et al. teach that the aerosolized inhaler can be delivered in a variety of different devices that involve a valve to release the formulation (see paragraph 118-120; addresses claim 77), such as a pressurized metered dose inhaler containing a solution or suspension of the drug in a propellant such as CFC, HFC or fluorocarbon (see paragraph 121; addresses claim 78).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Conferees:

Art Unit: 1627

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